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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/665,883

09/19/2003

Chong-Sheng Yuan

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EXAMINER

HUTSON, RICHARD G

ART UNIT

PAPER NUMBER

1652

MAIL DATE

DELIVERY MODE

12/16/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/665,883	Applicant(s) YUAN, CHONG-SHENG	
	Examiner Richard G. Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 September 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>9/1/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/23/2009 has been entered.

Applicant's amendment of claims 1, 31, 39, 45, 50, 60 and 68, in the paper of 9/23/2009, is acknowledged. Claims 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72 are still at issue and are present for examination.

Applicants' arguments filed on 9/23/2009, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Art Unit: 1652

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was stated in the previous office action as it applied to previous claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72. In response to the rejection, applicants have amended claims 1, 31, 39, 45, 50, 60 and 68 and traverse the rejection as it applies to the newly amended claims.

Applicants submit their traversal in light of the amendments to the claims, and in view of the revised guidelines concerning compliance with the written description requirement. Applicants submit that the claims as amended recite "the amino acid sequence of SEQ ID NO: 1" (or SEQ ID NO:2 or 3) and this definitively recites a particular amino acid sequence that should be interpreted by the office as the amino acid sequence of SEQ ID NO:1 (or SEQ ID NO:2 or 3), but not as any amino acid sequence fragment of SEQ ID NO: 1.

Applicants further note that they have amended the claim to remove the term "derivative" and now the claims recite that the second peptidyl fragment comprises the amino acid sequence of SEQ ID NO:2 or comprises the amino acid sequence of SEQ ID NO:2 having a conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2.

Art Unit: 1652

Applicants submit that the pending claims are limited structurally with respect to SEQ ID NO:2, and encompass conservative amino acid substitutions of SEQ ID NO:2 that retain at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2.

Applicants' note their previous comments regarding the knowledge and skills of a person of ordinary skill in the art relating to conservative amino acid substitutions, testing of conservatively substituted peptides, and the well-known structure-function correlation data for Hal2p that had been published at the time the application had been filed are incorporated herein in their entirety.

Applicants maintain that the pending claims are concordant with Example 11B of the written description guidelines, since the claims place structural limitations relevant to SEQ ID NO:2.

Applicant's amendment of the claims and applicants complete argument is acknowledged and has been carefully considered, however, is found nonpersuasive for the reasons previously made of record and for those repeated herein.

It is noted that applicants recitation of "the amino acid sequence of SEQ ID NO: 1" (or SEQ IDNO:2 or 3)" does not read on fragments of these sequences and is not an issue in the current rejection.

Applicants amendment of the claims to remove the term "derivative" is acknowledged and it is further acknowledged that the claims continue to recite that the second peptidyl fragment comprises the amino acid sequence of SEQ ID NO:2 or comprises the amino acid sequence of SEQ ID NO:2 having a conservative amino acid

Art Unit: 1652

substitution, wherein the substituted peptidyl fragment retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. While it is acknowledged that the pending claims are limited structurally with respect to SEQ ID NO:2, and encompass conservative amino acid substitutions of SEQ ID NO:2 that retain at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2, the claims remain rejected because applicants have not placed any limitation upon the number of conservative amino acid substitutions that may be made to SEQ ID NO:2. Thus applicants claimed chimeric proteins continues to comprise an enormous number of species, such that the disclosure of SEQ ID NO:2 is insufficient to adequately describe the claimed genus of variants of SEQ ID NO:2 having at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2.

Given this lack of representative species, beyond SEQ ID NO:2, as encompassed by the full breadth of the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric protein having nucleotidase activity comprising the amino acid sequence of

Art Unit: 1652

SEQ ID NO: 4, does not reasonably provide enablement for any chimeric protein having the enzymatic activity of a nucleotidase, comprising any peptidyl fragment comprising a bacterial leader sequence comprising the amino acid sequence set forth in SEQ ID NO: 1, any peptidyl fragment comprising SEQ ID NO:2 having an unlimited number of conservative amino acid substitutions wherein the peptidyl fragment retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2 and a peptidyl fragment comprising an amino acid sequence having as set forth in SEQ ID NO: 3 and methods of methods of their use, encompassed by these claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. invention.

This rejection was stated in the previous office action as it applied to previous claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72. In response to the rejection, applicants have amended claims 1, 31, 39, 45, 50, 60 and 68 and traverse the rejection as it applies to the newly amended claims.

Applicants submit that the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Applicants submit that experimentation is not considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance regarding the direction of experimentation - time and difficulty are not determinative of undue experimentation if the experimentation is routine.

Applicants submit that in order to make an enablement rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Applicants submit that as discussed previously and above, the art of preparing a polypeptide with a conservative amino acid mutation compared to another polypeptide having a fully defined sequence and a certain type of known biological activity was well-settled and routine at the time the present application was filed.

Applicants submit that in view of the amendments to the claims, Applicants submit that the claims meet the enablement requirement. The claims as amended recite that the second peptidyl fragment comprises the amino acid sequence of SEQ ID NO:2 or comprises the amino acid sequence of SEQ ID NO:2 having a conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2.

Applicants submit that compliance with 35 U.S.C. § 112, first paragraph enablement does not require that specific portions of any amino acid sequence be identified and it should not require undue experimentation to determine those portions of the sequence that are capable of mediating a biological function similar to that mediated by the protein of SEQ ID NO:2 having a conservative amino acid substitution.

Applicants submit that nothing more than objective enablement is required, and it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. Some experimentation is allowed as long as it is not undue.

Applicants submit that as an illustration, in the recent *Kubin* appeal stemming from U.S. Appl. No. 09/667,859, the exemplary claim recited "[a]n isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48." Applicants submit that the Board of Patent Appeals and Interferences overturned the enablement rejection while concluding that "[t]he amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine [because] [t]he techniques to do so were well known to those skilled in the art." *Ex parte Kubin*, Appeal No. 2007-0819, at 14 (BPAI May 31, 2007).

Applicants submit that as discussed previously, the art of preparing a polypeptide with a conservative amino acid mutation compared to another polypeptide having a fully defined sequence and a certain type of known biological activity was well-settled and routine at the time the present application was filed. The specification expressly describes methods by which such polypeptides having conservative amino acid mutations can be prepared without any undue experimentation. For example, the specification teaches the types of amino acid substitutions that may be used to achieve functional equivalence (paragraph [0018]).

Thus, Applicants maintain that the specification provides reasonable guidance to the skilled artisan regarding how to make and use the invention, including providing sufficient guidance on protein structure and sufficient guidance on methods for designing variant proteins having a desired activity. Accordingly, Applicants respectfully submit that the present claims are fully enabled by the specification to overcome the rejection under 35 U.S.C. § 112, first paragraph.

Applicant's amendment of the claims and applicants complete argument is acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously made of record and repeated herein.

Applicants continue to argue that the rejection under 35 U.S.C. §112, first paragraph is not proper because the specification teaches the complete amino acid sequence of SEQ ID NO:2, and protocols for testing for biological activity of conservative substitutions of SEQ ID NO:2 are within the skill of the ordinary artisan. This is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., comprising conservative amino acid substitutions of SEQ ID NO:2) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. While applicants disclosure of SEQ ID NO:2 and means of testing for the claimed activity are known, it continues that applicants claims are such that there is virtually no structural limitations required of the claimed variant of SEQ ID NO:2. Without such guidance one of ordinary skill would be reduced to the

Art Unit: 1652

necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2; (B) the general tolerance of SEQ ID NO:2 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any 3'(2'),5'-bisphosphonate residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants useful as the claimed chimeric 3'(2'),5'-bisphosphonates, requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims with such minor structural limitations, clearly it would constitute **undue** experimentation to arrive at and use the extreme number of encompassed polypeptides. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within

Art Unit: 1652

several hundred thousand or up to about a million inactive mutants as is the case for the claims limited to 95% identity (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the claims to 90% or less identity would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required by the breadth of the current claims, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the 3'(2'),5'-bisphosphate nucleotidase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable, it would require undue experimentation for one skilled in the art to arrive at the majority of those chimeric proteins having the enzymatic activity of a nucleotidase, comprising any peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence set forth in SEQ ID NO: 1, any peptidyl fragment comprising any polypeptide having a conservative amino acid substitution of SEQ ID NO:2 and retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2 and a peptidyl fragment comprising an amino acid sequence having as set forth in SEQ ID NO: 3.

With regard to applicants argument regarding the recent *Kubin* appeal stemming from U.S. Appl. No. 09/667,859, wherein the exemplary claim recited "[a]n isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.", applicants are reminded that applicants claims and disclosure as well as the factors to be considered in determining whether undue experimentation is required, are different from those considered in the *Kubin* decision. These of course are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Of primary importance in the determination of the enablement of applicants claimed chimeric proteins are the extreme breadth of the claims and the resultant quantity of experimentation necessary to enable such a large number of variations. While in *Kubin* the breadth of the claims was limited to those having 80% identity to amino acids 22-221 of SEQ ID NO:2 and able to bind to CD48 (roughly 40 amino acid changes of amino acids 22-221 of SEQ ID NO:2), applicants claims are limited to any number of changes of SEQ ID NO:2, with a conservative amino acid change, while maintaining 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. This is potentially greater than 350 amino acid changes that are encompassed by the breadth of applicant's claims and thus given this extreme breadth it would take considerable

Art Unit: 1652

experimentation to arrive at this number of SEQ ID NO:2 mutants thus resulting in undue experimentation.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any chimeric protein having the enzymatic activity of a nucleotidase, comprising polypeptide having a conservative amino acid substitution of SEQ ID NO:2 and retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2 and methods of their use. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides and methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1652

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rg
12/8/2009

/Richard G Hutson/
Primary Examiner, Art Unit 1652